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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/267,719	BURKS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2004; 9/19/00*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/00*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 26-44 are pending and are being acted upon in this Office Action.

2. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underling or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-Reference to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on a compact disc (see 37 CFR 1.52(e)(5)).
(e) Background of the Invention.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

3. A substitute specification including the claims is required pursuant to 37 CFR 1.125(a) because pages 24 through 107 of the specification are various slide presentations and render it difficult to consider the application and to arrange the papers for printing or copying, 37 CFR 1.125. A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and (c) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

4. The drawings, filed 3/11/99, are not approved because of different margin, line with different thickness, font size and inconsistency throughout the set of drawings. Further, color photographs and color drawings (FIG 3 and 5) are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states: The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee. Color photographs will be accepted if the conditions for accepting color drawings have been satisfied. Appropriate action is required.

5. The title of the invention "Tertiary structure of peanut allergen ARA H1" has nothing to do with claimed invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

6. The abstract of the disclosure is objected to because it exceeds the limits of 150 words. Correction is required. See MPEP § 608.01(b). Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of treating an individual to reduce the clinical response to peanut allergen Ara h1 comprising administering to the individual a modified peanut allergen Ara h1 having at least one of the hydrophobic amino acids located in the middle of the IgE epitope selected from the group consisting of amino acid residues 25-34 of SEQ ID NO: 1, amino acid residues 48-57 of SEQ ID NO: 1, amino acid residues 65-74 of SEQ ID NO: 1, amino acid residues 89-98 of SEQ ID NO: 1, amino acid residues 107-116 of SEQ ID NO: 1, amino acid residues 123-132 of SEQ ID NO: 1, amino acid residues 134-143 of SEQ ID NO: 1, amino acid residues 143-152 of SEQ ID NO: 1, amino acid residues 294-303 of SEQ ID NO: 1, amino acid residues 311-320 of SEQ ID NO: 1, amino acid residues 325-334 of SEQ ID NO: 1, amino acid residues 344-353 of SEQ ID NO: 1, amino acid residues 393-402 of SEQ ID NO: 1, amino acid residues 409-418 of SEQ ID NO: 1, amino acid residues 498-507 of SEQ ID NO: 1, amino acid residues 525-534 of SEQ ID NO: 1, amino acid residues 539-348 of SEQ ID NO: 1, amino acid residues 551-560 of SEQ ID NO: 1, amino acid residues 559-568 of SEQ ID NO: 1 and amino acid residues 578-587 of SEQ ID NO: 1 wherein the IgE epitopes have been substituted for Ala or Met that lead to loss of IgE binding as disclosed on page 24, line16-18; and page 28, line 6-9, **does not** reasonably provide enablement for a method of treating an individual to reduce the clinical response to *all* modified protein allergen, or all modified food allergen or all modified peanut allergen as set forth in claims 22-46. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the claim encompasses all modified protein allergen, all modified food allergen and all modified peanut allergens wherein at least any one amino acid has been modified so that the IgE binding is reduced, said modified allergen wherein at least any one amino acid has

been modified in all IgE epitopes of all unmodified protein allergen wherein the unmodified allergen is obtain from legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grass, tress, weeds, mammals, and natural latexes.

The specification discloses only a method treating peanut allergy using the modified peanut allergens Ara h1, Ara h2 and Ara h3 such as the ones disclosed on page 24, lines 16-18; and page 28, line 6-9. The modified peanut allergen Ara h1 has at least one of the hydrophobic amino acids located in the middle of the IgE epitope substituted for Ala or Met that lead to loss of IgE binding wherein the IgE epitope is selected from the group consisting of amino acid residues 25-34 of SEQ ID NO: 1, amino acid residues 48-57 of SEQ ID NO: 1, amino acid residues 65-74 of SEQ ID NO: 1, amino acid residues 89-98 of SEQ ID NO: 1, amino acid residues 107-116 of SEQ ID NO: 1, amino acid residues 123-132 of SEQ ID NO: 1, amino acid residues 134-143 of SEQ ID NO: 1, amino acid residues 143-152 of SEQ ID NO: 1, amino acid residues 294-303 of SEQ ID NO: 1, amino acid residues 311-320 of SEQ ID NO: 1, amino acid residues 325-334 of SEQ ID NO: 1, amino acid residues 344-353 of SEQ ID NO: 1, amino acid residues 393-402 of SEQ ID NO: 1, amino acid residues 409-418 of SEQ ID NO: 1, amino acid residues 498-507 of SEQ ID NO: 1, amino acid residues 525-534 of SEQ ID NO: 1, amino acid residues 539-348 of SEQ ID NO: 1, amino acid residues 551-560 of SEQ ID NO: 1, amino acid residues 559-568 of SEQ ID NO: 1 and amino acid residues 578-587 of SEQ ID NO: 1 (Table 1).

The specification does not teach how to make all modified protein allergen, and all modified food allergen mentioned above for a method of treating an individual to reduce the clinical response to all protein allergen, and all food allergen because there is insufficient guidance as to which amino acids such as 1-6, 1-5, 1-4, 1-3 or 1-2 amino acid residues within which IgE epitope of the full-length amino acid sequence of which unmodified protein allergen or food allergen is/are to be substituted for which undisclosed amino acids without the amino acid sequence. There is insufficient guidance as how to make *all* modified protein allergen from unmodified protein allergen such as any legumes, milks, grains, eggs, fish, crustaceans, mollusks, and all modified food allergen from unmodified food allergen such as wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp whose amino acid sequence is "substantially" identical to any unmodified protein allergen or any food allergen. The specification does not define the term "substantially". The modified protein allergen or modified food allergen could be 50% differs from the unmodified protein allergen or food allergen and still be substantially identical to said unmodified protein or food allergen. There is insufficient guidance as where are

all the IgE epitopes within the full-length sequence of all protein allergen, and all food allergen. There is insufficient working examples demonstrating that all modified protein and all food allergen after modification by substitution, deletion, addition would retain the ability to activate T cells, bind IgG and initiate a Th-1 type response, much less reducing IgE binding for a method of treating all allergy. Given the indefinite number of modified protein allergen and food allergen, the specification fails to provide guidance as to which type of amino acids within the IgE binding epitopes of *any* of the undisclosed protein allergen and food allergen mentioned above can be deleted, substituted or added, and whether the resulting modified allergen would decrease IgE binding, in turn, would be useful for treating all allergy. There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Attwood *et al* teaches that protein function is context-dependent; the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable and knowing structure alone will not inherently tell us function (See figure, entire document).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Wal *et al* teach proteins (CMP) involved in milk allergy are numerous and heterogeneous, with very few structural or functional common features. This heterogeneity is complicated by their genetic polymorphism, resulting in several variants for each protein. These variants are characterized by point substitutions of amino acids or by deletions of peptide fragments of varying size or by post-translational modifications such as phosphorylation or glycosylation. All of these modifications may affect allergenicity. No common molecular structure can be associated with allergenicity, although some homologous regions such as casein phospho-peptides can explain an IgE cross-reactivity. Three-dimensional structure is an important feature in CMP allergenicity but denatured and linear epitopes are also involved. Epitopes are numerous and widely spread along the CMP molecule. They may be located in hydrophobic parts of the molecule where they are inaccessible for IgE antibodies in the native conformation of the protein but become bioavailable after digestive processes. Peptides as short as ca. 12-14 amino acid residues may account for a significant part of the allergenicity of the whole molecule.

Cocco *et al* teach a method of identifying the critical amino acids (AAs) for immunoglobulin E (IgE) binding within the major B-cell epitopes of alpha(s1)-casein, a major cow's milk allergen. Cocco et al teach mutational analysis of the IgE-binding epitopes, peptides of 10-14 AAs in length were synthesized on a derivatized cellulose membrane with single or multiple AA substitutions. Membranes were immunolabeled with pooled sera from 15 cow's-milk-allergic patients and with 8 individual sera. The results show that with the pooled sera, substitution of a single AA led to complete abrogation of IgE binding to 2 of 8 peptides and diminished binding in the remainder. Substitution of multiple AAs led to an abrogation of binding in the remaining peptides. However, in 4 of the 8 peptides, the critical AA identified with pooled sera did not result in significant reduction of IgE binding with 1 or more individual patients, indicating the B-cell-epitope heterogeneity of allergen. Cocco *et al* teach that "engineered" recombinant allergen as vaccine might still provoke adverse reactions in some patients (See page 436, col. 2, first paragraph, in particular).

Fasler *et al* teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with either a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al* teach a modified allergen from peanut Ara h1 where substituting the immunodominant IgE binding epitope of Ara h1 at position 1, 3, 4 and 17 for alanine or glycine would reduced IgE binding. However, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al* teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an

alanine for a single amino acid residue. Again, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). As such, the specification merely extends an invitation for one skill in the art for further experimentation to arrive at the claimed method. Until the specific amino acids substitution within all IgE epitopes of all protein allergen, and all food allergen obtained from unmodified protein allergen such as *any* dust, *any* grasses, *any* trees, *any* weeds, *any* mammals, natural latexes, *any* legumes, *any* milks, *any* eggs, *any* fish, *any* crustaceans, *any* mollusks, *any* insects, *any* molds, *any* wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp have been identified, the claimed method of treating any individual to reduce the clinical response to all protein allergen, or all food allergen is not enabled.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. As such, further research would be required. In view of the quantity of experimentation necessary, the insufficient number of working examples, the unpredictability of the art, the insufficient guidance and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) all modified protein allergen that has amino acid sequence that is "substantially identical" to that of any unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope in the claimed method of treating an individual to reduce the clinical response to any protein allergen, wherein at least one IgE eptiope contains 1-6, 1-5, 1-4, 1-3 or 1-2 amino acid residues have been modified compared with the unmodified allergen for the claimed method, (2) all modified protein allergen wherein at least one amino acid has been modified in all the IgE epitopes of the unmodified protein allergen for the claimed method, (3) all modified protein allergen wherein at least one IgE epitope of the undisclosed protein allergen has been modified by

substitution such as at least one hydrophobic amino acid in the at least IgE epitope of the undisclosed unmodified protein allergen has been substituted by any natural or hydrophilic amino acid, any modified protein allergen retains the ability to activates T cells, bind IgG or initiate a Th1-type response for the claimed method, (4) all modified protein derived from unmodified protein allergen obtained from *any* legumes, *any* milks, *any* eggs, *any* fish, *any* crustaceans, *any* mollusks, *any* insects, *any* molds, *any* dust, *any* grasses, *any* trees, *any* weeds, *any* mammals, or natural latexes for the claimed method, (5) all modified "food allergen" that has amino acid sequence that is "substantially identical" to that of any unmodified food allergen such as the ones obtained from *any* legumes, *any* milks, *any* eggs, *any* fish, *any* crustaceans, *any* mollusks, *any* insects, *any* molds, any wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp wherein at least one IgE eptiope contains 1-6, 1-5, 1-4, 1-3 or 1-2 amino acid residues have been modified compared with the unmodified allergen for the claimed method and (6) all modified peanut allergen such as Ara h1, Ara h2 and Ara h3 wherein at least one IgE eptiope contains 1-6, 1-5, 1-4, 1-3 or 1-2 amino acid residues have been modified compared with the unmodified allergen in the claimed method.

The specification discloses only a method treating peanut allergy using the modified peanut allergens Ara h1, Ara h2 and Ara h3 such as the ones disclosed on page 24, lines 16-18; and page 28, line 6-9. The modified peanut allergen Ara h1 has at least one of the hydrophobic amino acids located in the middle of the IgE epitope substituted for Ala or Met that lead to loss of IgE binding wherein the IgE epitope is selected from the group consisting of amino acid residues 25-34 of SEQ ID NO: 1, amino acid residues 48-57 of SEQ ID NO: 1, amino acid residues 65-74 of SEQ ID NO: 1, amino acid residues 89-98 of SEQ ID NO: 1, amino acid residues 107-116 of SEQ ID NO: 1, amino acid residues 123-132 of SEQ ID NO: 1, amino acid residues 134-143 of SEQ ID NO: 1, amino acid residues 143-152 of SEQ ID NO: 1, amino acid residues 294-303 of SEQ ID NO: 1, amino acid residues 311-320 of SEQ ID NO: 1, amino acid residues 325-334 of SEQ ID NO: 1, amino acid residues 344-353 of SEQ ID NO: 1, amino acid residues 393-402 of SEQ ID NO: 1, amino acid residues 409-418 of SEQ ID NO: 1, amino acid residues 498-507 of SEQ ID NO: 1, amino acid residues 525-534 of SEQ ID NO: 1, amino acid residues 539-348 of SEQ ID NO: 1, amino acid residues 551-560 of SEQ ID NO: 1, amino acid residues 559-568 of SEQ ID NO: 1 and amino acid residues 578-587 of SEQ ID NO: 1 (Table 1).

With the exception of the specific modified peanut allergen mentioned above for the claimed method of treating an individual to reduce the clinical response to peanut allergen, there

is insufficient written description about the structure associated with function of all modified "protein allergen", and all "modified food allergen" mentioned above without the amino acid sequence. Further, there is inadequate written description about which amino acids within which IgE epitope or all IgE epitopes of which protein allergen or food allergen wherein IgE eptiope contains which 1-6, 1-5, 1-4, 1-3 or 1-2 amino acid residues have been modified by amino acid substitution, deletion or addition. The specification does not define the term "substantially identical". Any modified protein allergen or food allergen that has 50% sequence identity to any unmodified protein allergen or food allergen would still be "substantially identical". Further, there is insufficient written description about all the IgE epitopes within the full-length sequence of all protein allergen, and all food allergen. There is insufficient written description about which amino acid within the full-length of which undisclosed protein allergen or food allergen to be substituted for which amino acid residues that would resulted in reducing IgE, which amino acid substitution would retain the ability to activate T cells, which amino acid substitution would retain a Th-1 type response, much less reducing IgE binding for a method of treating all allergy.

Finally, the specification discloses only modified peanut allergen such as the ones shown in Table 1, and the ones disclosed on page 24, lines 16-18; and page 28, line 6-9. Other than modified peanut allergen for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus of modified protein allergen, and modified food allergen. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. Claims 26-44 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "method...wherein the *modified protein allergen* has an amino acid sequence that is substantially identical to that of an unmodified protein allergen except that at least one amino acid has been modified in at least one IgE epitope so that IgE binding to the modified protein allergen

is reduced as compared with IgE binding to the unmodified protein allergen, the at least one IgE epitope being one that is recognized when the unmodified protein allergen is contacted with serum IgE from an individual that is allergic to the unmodified protein allergen" in Claim 26 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ....wherein at least one amino acid has been modified in *all the IgE epitope* of the unmodified protein allergen" in claim 27 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method wherein at least one hydrophobic amino acid in the at least one IgE epitope of the unmodified protein allergen has been substituted by a neutral or hydrophilic amino acid" in claim 31 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ...wherein the modified protein allergen retains the ability to activate T cells" in claim 32 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ... wherein the modified protein allergen retains the ability to bind IgG" in claim 33 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ... wherein the modified protein allergen retains its ability to initiate a Th1-type response" in claim 34 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ... wherein the unmodified protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals and natural latexes" in claim 36 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ...preparing at least one modified protein allergen whose amino acid sequence that is substantially identical to that of the unmodified protein allergen..." in claim 37 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

"A method ... of treating ...to a food allergen... wherein the modified food allergen has an amino acid sequence that is substantially identical to that of the unmodified food allergen..."

in claim 38 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ...wherein the unmodified food allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks" in claim 39 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method ...wherein the unmodified food allergen is obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel nut, soybean and shrimp" in claim 40 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method of claims 26, claim 38 or claim 41 wherein the at least one IgE epitope contains 1-6, 1-5, 1-4, 1-3 or 1-2 amino acid residues that are modified as compared with the unmodified allergen" in claim 43 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

The "method of claims 26, claim 38 or claim 41 wherein binding by serum IgE to the at least one epitope is reduced for the modified allergen to less than about 1% of that observed to the unmodified allergen" in claim 44 represents a departure from the specification and the claims as originally filed. Applicant has not pointed out the support for said phrase.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claims 26-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "substantially identical" in claims 26, 38 and 41 is ambiguous and indefinite because any modified protein allergen or food allergen that has 50% differences sequence identical to any unmodified protein allergen or food allergen would still be "substantially identical" since the specification does not defined the term "substantially identical". One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 26, 28, and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferreira *et al* (Int Arch Allergy 113(1-3): 125-27, May 1997; PTO 892).

Ferreira *et al* teaches a method of treating allergy in individual to reduce the clinical response to a protein allergen such as Bet v1 from tree pollen by administering to the individual a modified protein such as birch pollen allergen isoform d that has amino acid sequence that is substantially identical to that of an unmodified recombinant birch pollen allergen except that the modified Bet v1 has reduced IgE binding from allergic patients (See abstract, in particular). The reference method wherein the modified allergen retains the ability to activate T cells (See abstract, in particular). Ferreira *et al* teaches high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular). Claim 28 is included in this rejection because the pooled IgE sera from 30 allergic patients are at least two patients (See materials and methods, in particular). Claims 32-34 are included in this rejection because the reference modified protein inherently retains the ability to activate T cells, bind IgG and initiate a Th1-type response due to the modified allergen amino acid sequence is substantially identical to the unmodified birch pollen allergen. Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferreira *et al* (Int Arch Allergy 113(1-3): 125-27, May 1997; PTO 892) in view of Suphioglu *et al* (Mol Immunol 35: 293-305, July 1998; PTO 892) or Noguchi *et al* (International Archives of Allergy and Immunology 110(4): 380-7, Aug 1996; PTO 892).

The teachings of Ferreira have been discussed supra.

The invention in claim 35 differs from the teachings of the reference only in that the method wherein the modified protein allergen is a portion of the unmodified protein allergen.

The invention in claim 36 differs from the teachings of the reference only in that the method wherein the unmodified protein allergen is obtained from grasses or dust.

Suphioglu *et al* teaches modified protein allergen such as Lol p5 peptide 34 from unmodified protein allergen such as rye grass pollen Lol p5 (See entire document, abstract, in particular). The reference modified protein allergen is a portion of the unmodified protein allergen such as amino acid residues 265-276 of the full length amino acid sequence of Lol p5 (See Table 1, in particular) having an amino acid substitution from Lys at position 275 to alanine (See page 301, Table 3, page 302, col. 1, paragraph 1, in particular). The reference modified protein allergen has reduced IgE binding (See page 303, col 2, paragraph 1, in particular) and is useful in immunotherapy (See abstract, page 303, col. 2, second paragraph, in particular).

Noguchi *et al* teach various modified allergens such as rDer f2 from dust mite that have at least one amino acid substitution in the IgE binding epitope, in which Asp 7 was replaced by Ala, both Cys 8 and Cys199 were replaced by Ser (See abstract, in particular). The reference modified dust allergens obtained from unmodified dust allergens have reduced IgE binding almost to a background level with the sera from young asthmatic children (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the modified protein allergen or 'hypogenic allergen' such as Bet v1 as taught by Ferreira *et al* for the modified protein allergen from grass pollen such as Lol p5 as taught by Suphioglu *et al* or the modified dust mite allergen rDer f2 as taught by Noguchi et al for a method of treating an individual to reduce the clinical response to protein allergen as taught by Ferreira *et al* and Suphioglu *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Suphioglu *et al* teaches modified protein allergen with reduced IgE binding (See page 303, col 2, paragraph 1, in particular) is useful in immunotherapy considering their reduced anaphylacogeinic potential (See abstract, page 303, col. 2, second paragraph, in particular). Noguchi *et al* teach modified allergens such as rDer f2 from dust mite that have at least one amino acid substitution in the IgE binding epitope, in which Asp 7 was replaced by Ala, and both Cys 8 and Cys199 were replaced by Ser have reduced IgE binding (See abstract, in particular). Ferreira *et al* teaches high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular).

18. Claims 26-31, 35-39, and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks *et al* (Eur J Biochem 245: 334-339, Feb 1997; PTO 1449) in view of Ferreira *et al* (Int Arch Allergy 113(1-3): 125-27, May 1997; PTO 892).

Burks *et al* teach a modified protein allergen such as peanut (food) allergen Ara h1 whose amino acid sequence is substantially identical to that of an unmodified food allergens such as peanut Ara h1 except that one amino acid has been modified in one of the IgE epitope so that IgE binding to the reference modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen, and the reference IgE epitope is recognized by 15 individuals who is allergic to the unmodified peanut allergen (See entire document, Materials and Methods, Fig 6, in particular). The reference modified protein or food allergen is based on a protein obtained from the legumes family. The reference modified protein allergen whose immunodominant IgE epitope of unmodified Ara h1 protein or portion thereof can be mutated to non-IgE binding epitopes by a single amino acid changes (See Fig. 6-7, in particular). The modified reference

allergen is mutated in the center of one or more IgE binding epitopes by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites with a neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, in particular). The modified allergen is made by the process of identifying one or more IgE binding sites in an allergen, mutating one or more amino acid in an IgE binding site, screening for IgE binding to the mutated allergen and selecting the modified allergens with the least binding to IgE (See Fig 2 and 3; page 247; page 246 for IgE-binding assay, in particular). The reference further teaches there are at least 23 different IgE binding epitopes on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of a protein (See Figs 1-3, Fig 6, page 339, column 1, in particular). Burks *et al* teach it is possible to mutate the Ara h1 allergen to a protein so that it no longer binds IgE and this could be used to replace its allergenic homologue in the peanut genome to develop a hypoallergenic peanut and for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). The reference modified-allergen has reduced IgE binding to less than about 1% of that observed to the unmodified allergen (See Fig 4 and 5, in particular). The reference modified protein allergen having at least one modified amino acid in all the IgE epitope of the unmodified peanut allergen would have expected to be hypoallergenic and would be useful to blunt the allergic reactions in sensitive individual (See page 339, col. 1, last paragraph, in particular).

The claimed invention in claim 26 differ from the teachings of the reference only in that a method of treating an individual to reduce the clinical response to a protein allergen by administering to the individual a modified protein allergen.

The claimed invention in claim 38 differ from the teachings of the reference only in that a method of treating an individual to reduce the clinical response to a protein allergen by administering to the individual a modified food allergen.

The claimed invention in claim 41 differ from the teachings of the reference only in that a method of treating an individual to reduce the clinical response to a protein allergen by administering to the individual a modified peanut allergen.

The claimed invention in claim 42 differ from the teachings of the reference only in that a method wherein the unmodified peanut allergen is Ara h1.

Ferreira *et al* teaches a method of treating allergy in individual to reduce the clinical response to a protein allergen such as Bet v1 from tree pollen by administering to the individual a

modified protein such as birch pollen allergen isoform d that has amino acid sequence that is substantially identical to that of an unmodified recombinant birch pollen allergen except that the modified Bet v1 has reduced IgE binding from allergic patients (See abstract, in particular). The reference method wherein the modified allergen retains the ability to activate T cells (See abstract, in particular). Ferreira *et al* teaches high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat an individual to reduce the clinical response to peanut allergy by substituting the modified protein allergen such as Bet v1 as taught by Ferreira *et al* for the modified protein allergen from peanut such as Ara h1 as taught by Burks *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Burks *et al* teaches modified peanut allergen with reduced IgE binding would expected to hypoallergenic and would be useful to blunt the allergic reactions in sensitive individual (See page 339, col. 1, last paragraph, in particular). Ferreira *et al* teach that hypoallergenic recombinant allergen is useful for allergen specific immunotherapy (See abstract, in particular) and high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular).

19. Claims 26-31, 35-39, and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley *et al* (Archives of Biochem and Biosphysics 342(2): 244-253, June 1997; PTO 892) in view of Ferreira *et al* (Int Arch Allergy 113(1-3): 125-27, May 1997; PTO 892).

Stanley *et al* teach a modified protein allergen such as peanut (food) allergen Ara h2 such as peptide 7 whose amino acid sequence is substantially identical to that of an unmodified food allergens such as peanut Ara h2 (See Fig 1, in particular) except that one amino acid has been modified in one of the IgE epitope so that IgE binding to the reference modified food allergen is reduced as compared with IgE binding to the unmodified peanut allergen, and the reference IgE epitope is recognized by 15 individuals who is allergic to the unmodified peanut allergen (See entire document, Materials and Methods, Table III, Fig 5, in particular). The reference modified

protein or food allergen is based on unmodified protein obtained from legumes, in which peanut is part of the family. The reference modified protein allergen such as peptide 7 can be mutated to non-IgE binding epitope by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites (See Fig. 5, in particular). The modified allergen is made by the process of identifying one or more IgE binding sites in an allergen (See isolation and amino acid sequence analysis of peanut allergen Ara h2 on page 245, col. 1, page 248, col. 2, identification of immunodominant Ara h2 epitopes, in particular), mutating one or more amino acid in an IgE binding site (See page 251, col. 1, second paragraph, in particular), screening for IgE binding to the mutated allergen and selecting the modified allergens with the least binding to IgE (See materials and methods, Fig 5, IgE-binding assay, in particular). The reference modified-allergen has reduced IgE binding to less than about 1% of that observed to the unmodified allergen (See Fig 5, in particular). The reference modified allergen peptide 7 is a portion of the unmodified peanut allergen and is expected to improved diagnostic and therapeutic approaches to peanut hypersensitivity (See abstract, in particular). Stanley *et al* teaches modified peanut allergen such as Ara h2 with reduced IgE binding would expected to be hypoallergenic and would be useful to blunt the allergic reactions in sensitive individual (See page 252, col. 1, last paragraph, in particular).

The claimed invention in claim 26 differ from the teachings of the reference only in that a method of treating an individual to reduce the clinical response to a protein allergen by administering to the individual a modified protein allergen.

The claimed invention in claim 38 differ from the teachings of the reference only in that a method of treating an individual to reduce the clinical response to a protein allergen by administering to the individual a modified food allergen.

The claimed invention in claim 41 differ from the teachings of the reference only in that a method of treating an individual to reduce the clinical response to a protein allergen by administering to the individual a modified peanut allergen.

The claimed invention in claim 42 differ from the teachings of the reference only in that a method wherein the unmodified peanut allergen is Ara h2.

Ferreira *et al* teaches a method of treating allergy in individual to reduce the clinical response to a protein allergen such as Bet v1 from tree pollen by administering to the individual a modified protein such as birch pollen allergen isoform d that has amino acid sequence that is substantially identical to that of an unmodified recombinant birch pollen allergen except that the

modified Bet v1 has reduced IgE binding from allergic patients (See abstract, in particular). The reference method wherein the modified allergen retains the ability to activate T cells (See abstract, in particular). Ferreira *et al* teaches high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat an individual to reduce the clinical response to peanut allergy by substituting the modified protein allergen such as Bet v1 as taught by Ferreira *et al* for the modified protein allergen from peanut such as Ara h2 as taught by Stanley *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Stanley *et al* teaches modified peanut allergen such as Ara h2 with reduced IgE binding would expected to hypoallergenic and would be useful to blunt the allergic reactions in sensitive individual (See page 252, col. 1, last paragraph, in particular). Ferreira *et al* teach that hypoallergenic recombinant allergen is useful for allergen specific immunotherapy (See abstract, in particular) and high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular).

20. Claims 36, and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks *et al* (Eur J Biochem 245: 334-339, Feb 1997; PTO 892) in view of Ferreira *et al* (Int Arch Allergy 113(1-3): 125-27, May 1997; PTO 892) as applied to claims 26-31, 35-39, and 41-44 mentioned above and further in view of US Pat No US Pat No. 5,449,669 (Sept 1995, PTO 892).

The combined teachings of Burks et al and Ferreira *et al* have been discussed supra.

The invention in claim 36 and 39 differs from the combined teachings of the references only in that the method wherein the unmodified protein allergen is obtained from crustaceans.

The invention in claim 40 differs from the teachings of the reference only in that the method wherein the unmodified protein allergen is shrimp.

The 5,449,669 patent teaches unmodified allergen such as Pen i I from crustaceans such as shrimp (See Fig 1, in particular) and various modified allergen such as peptides 6 and peptide 9 from Pen I I or tropomyosin (See Table II, Col 12, lines 41, in particular). The reference

unmodified and modified allergens are useful in the treatment of allergy (desensitization) of individual that are allergic to shrimp and other crustacean such as lobster, prawn, and crab (See abstract, col. 12, lines 44-45, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made treat an individual to reduce the clinical response to shrimp by substituting the modified protein allergen such as Bet v1 as taught by Ferreira *et al* or the peanut allergen as taught by Burks et al for the modified allergen derived from unmodified protein allergen such as Pen i I from crustaceans such as shrimp as taught by the '669 patent for a method of treating an individual to reduce the clinical response to protein allergen as taught by Ferreira *et al,* Burks *et al* and the '669 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the 5,449,669 patent teaches modified allergen from unmodified allergen such as shrimp are useful in the treatment of allergy (desensitization) of individual that are allergic to shrimp and other crustacean such as lobster, prawn, and crab (See abstract, col. 12, lines 44-45, in particular). Ferreira *et al* teach that hypoallergenic recombinant allergen is useful for allergen specific immunotherapy (See abstract, in particular) and high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular).

21. Claims 36, and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley *et al* (Archives of Biochem and Biosphysics 342(2): 244-253, June 1997; PTO 892) in view of Ferreira *et al* (Int Arch Allergy 113(1-3): 125-27, May 1997; PTO 892) as applied to claims 26-31, 35-39, and 41-44 mentioned above and further in view of US Pat No US Pat No. 5,449,669 (Sept 1995, PTO 892).

The combined teachings of Stanley et al and Ferreira *et al* have been discussed supra.

The invention in claim 36 and 39 differs from the combined teachings of the references only in that the method wherein the unmodified protein allergen is obtained from crustaceans.

The invention in claim 40 differs from the teachings of the reference only in that the method wherein the unmodified protein allergen is shrimp.

The 5,449,669 patent teaches unmodified allergen such as Pen i I from crustaceans such as shrimp (See Fig 1, in particular) and various modified allergen such as peptides 6 and peptide 9 from Pen I I or tropomyosin (See Table II, Col 12, lines 41, in particular). The reference unmodified and modified allergens are useful in the treatment of allergy (desensitization) of individual that are allergic to shrimp and other crustacean such as lobster, prawn, and crab (See abstract, col. 12, lines 44-45, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made treat an individual to reduce the clinical response to shrimp by substituting the modified protein allergen such as Bet v1 as taught by Ferreira *et al* or the peanut allergen as taught by Stanley et al for the modified allergen derived from unmodified protein allergen such as Pen i I from crustaceans or shrimp as taught by the '669 patent for a method of treating an individual to reduce the clinical response to protein allergen as taught by Ferreira *et al,* Stanley *et al* and the '669 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the 5,449,669 patent teaches modified allergen from unmodified allergen such as shrimp are useful in the treatment of allergy (desensitization) of individual that are allergic to shrimp and other crustacean such as lobster, prawn, and crab (See abstract, col. 12, lines 44-45, in particular). Ferreira *et al* teach that hypoallergenic recombinant allergen is useful for allergen specific immunotherapy (See abstract, in particular) and high doses of the hypoallergenic recombinant allergen would induce a modulation of the T cell response but without the risk of allergic side effects during the treatment (See page 127, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

24. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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